ORIGINAL ARTICLE

HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014–2015

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ABSTRACT

BACKGROUND

In January 2015, a total of 11 new diagnoses of human immunodeficiency virus (HIV) infection were reported in a small community in Indiana. We investigated the extent and cause of the outbreak and implemented control measures.

METHODS

We identified an outbreak-related case as laboratory-confirmed HIV infection newly diagnosed after October 1, 2014, in a person who either resided in Scott County, Indiana, or was named by another case patient as a syringe-sharing or sexual partner. HIV polymerase (*pol*) sequences from case patients were phylogenetically analyzed, and potential risk factors associated with HIV infection were ascertained.

RESULTS

From November 18, 2014, to November 1, 2015, HIV infection was diagnosed in 181 case patients. Most of these patients (87.8%) reported having injected the extended-release formulation of the prescription opioid oxymorphone, and 92.3% were coinfected with hepatitis C virus. Among 159 case patients who had an HIV type 1 *pol* gene sequence, 157 (98.7%) had sequences that were highly related, as determined by phylogenetic analyses. Contact tracing investigations led to the identification of 536 persons who were named as contacts of case patients; 468 of these contacts (87.3%) were located, assessed for risk, tested for HIV, and, if infected, linked to care. The number of times a contact was named as a syringe-sharing partner by a case patient was significantly associated with the risk of HIV infection (adjusted risk ratio for each time named, 1.9; P<0.001). In response to this outbreak, a public health emergency was declared on March 26, 2015, and a syringe-service program in Indiana was established for the first time.

CONCLUSIONS

Injection-drug use of extended-release oxymorphone within a network of persons who inject drugs in Indiana led to the introduction and rapid transmission of HIV. (Funded by the state government of Indiana and others.)

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A complete list of the members of the Indiana HIV Outbreak Investigation Team is provided in the Supplementary Appendix, available at NEJM.org.

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The epidemic of prescription opioid analgesic use and abuse in the United States over the past two decades[1] has led to a marked increase in the incidence of death from opioid analgesic poisoning, with a quadrupling of the incidence from 1999 through 2011.[2] In 2009, for the first time, deaths from drug overdose (37,004 deaths, of which 60% were related to the use of opioids) outnumbered deaths from motor vehicle accidents in the United States.[3,4] This epidemic of prescription opioid analgesic abuse has led to increases in the numbers of persons who inject drugs, as persons transition from oral use of opioids to insufflation (i.e., snorting or sniffing) to injection use.[5-8] Hepatitis C virus (HCV) is the most common infection transmitted through drug injection, and a large proportion of new HCV infections are associated with injection-drug use.[9-13] In the United States, the number of cases of acute HCV infection reported from 2010 through 2013 increased by 151%,[10] and these increases have occurred disproportionately among young persons, 30 years of age or younger, who reside in nonurban areas[14] east of the Mississippi River, particularly within central Appalachia.[15] These communities have also historically had a very low prevalence of human immunodeficiency virus (HIV) infection.[16]

On January 23, 2015, the Indiana State Department of Health (ISDH) began investigating a cluster of 11 newly diagnosed HIV infections, which was identified by an alert disease intervention specialist, among residents of a small rural community in Scott County,[17] where only 5 HIV infections had been diagnosed from 2004 through 2013 (Office of Clinical Data and Research, Division of HIV/STD, ISDH: unpublished data). All 11 HIV-infected persons reported having injected the extended-release formulation of the prescription opioid oxymorphone. An investigation that included contact tracing and phylogenetic analyses of HIV and HCV sequences was conducted to determine the extent and cause of this outbreak and to institute control measures.

Methods

Oversight

The investigation of this outbreak was part of a response to a public health emergency. As such, the investigation was approved by the Centers for Disease Control and Prevention (CDC) in accordance with federal human subjects protection regulations and CDC policies and procedures[18,19]; review by an institutional review board was not required. Informed consent for research was not obtained because the activity was determined not to be research. Routine consents for HIV testing (oral or written, depending on the setting) and for contact tracing (oral) were obtained. All the authors vouch for the integrity and completeness of the data and analyses.

Case Definition, Contact Tracing, and Case Finding

We defined an outbreak-related case as laboratory-confirmed HIV infection newly diagnosed after October 1, 2014, in a person who either resided in Scott County, Indiana (estimated population, 14,799 persons 18 to 65 years of age in 2014), or was named by another case patient as a syringe-sharing or sexual partner. A disease intervention specialist asked case patients to identify persons with whom they had shared syringes or had sex in the previous 12 months, as well as any social contacts who might benefit from HIV testing. Using this information, the disease intervention specialist located the contacts in the community and offered them point-of-care HIV testing. Diagrams of the connections between case patients and the contacts were made so that we could visualize the networks of syringe-sharing and sexual contacts (see the Supplementary Appendix, available with the full text of this article at NEJM.org). We interviewed case patients and contacts to ascertain information with respect to drug use and sexual behavior. Deidentified data were maintained in a password-protected and physically secured electronic database.

Screening for HIV and HCV Infection

Before this outbreak, free HIV testing had not been available in this community since a Planned Parenthood clinic closed in 2013. Five HIV testing sites were established in response to this outbreak. Initial point-of-care screening was conducted in most persons with the use of an oral fluid (OraQuick Advance Rapid HIV-1/2 Antibody Test, OraSure Technologies). Venous blood specimens from persons who had nonreactive point-of-care rapid tests were sent to a central labora-

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tory (ISDH Laboratories) to be tested for early and acute HIV infection with the use of a third-generation HIV enzyme immunoassay (VITROS Anti-HIV 1+2 Assay, Ortho Clinical Diagnostics) and a pooled HIV type 1 (HIV-1) RNA assay (Aptima HIV-1 RNA Qualitative Assay, Hologic) that included 256 specimens (estimated lower limit of quantification, 7680 HIV-1 copies per milliliter); if the pool tested positive, it was deconstructed to identify the individual positive specimen.[20] HIV infection was considered to be present if a point-of-care or laboratory HIV assay was reactive and was confirmed by either the Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) or an individual HIV-1 RNA test. The recency of the HIV infection was determined by means of avidity testing (modified Bio-Rad HIV-1/HIV-2 Plus O assay).[21] All venous blood specimens were also tested for HCV antibody (with the use of the VITROS Anti-HCV assay [Ortho Clinical Diagnostics]), hepatitis B virus (HBV) surface antigen (VITROS HBsAg assay, Ortho Clinical Diagnostics), and syphilis (Sure-Vue RPR, Fischer HealthCare). Additional details on screening for HIV and HCV infection are provided in the Methods section in the Supplementary Appendix.

MOLECULAR LABORATORY INVESTIGATION

HIV-1 RNA was extracted from serum or plasma with the use of a QIAamp viral RNA mini kit (Qiagen), according to the manufacturer's instructions. Partial polymerase (*pol*) sequences (approximately 915 bp) were amplified by means of polymerase chain reaction and sequenced as described previously.[22] For HIV-1 *pol* reference sequences, we used sequences associated with infections that were diagnosed in Indiana counties other than Scott County by the ISDH Laboratories, as well as sequences that we identified in a search of the GenBank database using Basic Local Alignment Search Tool (BLAST) software.[23] Sequences were aligned with the use of Molecular Evolutionary Genetics Analysis version 6.0 (MEGA6) software,[24] and we performed phylogenetic analysis using the program FastTree, version 2.1.[25] Trees were visualized with the use of FigTree software, version 1.4.[26] A phylogenetic cluster was defined when HIV-1 *pol* sequences shared nucleotide identity of greater than 97%, with a Shimodaira–Hasegawa probability of greater than 0.99. The presence of antiretroviral drug resistance mutations in the *pol* sequences was assessed with the use of the Stanford University HIV Drug Resistance database service Sierra, version 7.0.1.[27]

The HCV NS5B genomic region (300 bp) was amplified by polymerase chain reaction with in-house specific primers and was sequenced with the use of a BigDye chemistry sequencing kit, version 3.1 (Applied Biosystems), with an automated sequencer (ABI 3130xl genetic analyzer, Applied Biosystems), as described previously.[28] Maximum likelihood phylogenetic trees were constructed with the use of MEGA6 software.[24] The NS5B sequences were used to classify HCV strains into genotypes and subtypes by phylogenetic analysis with HCV NS5B reference sequences, which were obtained from the Division of Viral Hepatitis of the CDC.

STATISTICAL ANALYSIS

We used the chi-square test, Fisher's exact test, F-test, and the Kruskal–Wallis test to compare demographic variables and HIV risk factors between case patients and the contacts who were negative for HIV and had complete information. Variables that differed significantly according to HIV status were examined as potential risk factors; P values of less than 0.05 were considered to indicate statistical significance. Log-binomial regression modeling with stepwise backward elimination was used to estimate adjusted risk ratios. All analyses were conducted with the use of SAS software, version 9.3 (SAS Institute).

RESULTS

PATIENTS

From November 18, 2014, to November 1, 2015, we identified 181 outbreak-related HIV-1 infections. The first 3 cases were detected during routine HIV screening, and through the initial tracing of contacts, 8 more cases were diagnosed in syringe-sharing partners of these case patients. The number of new diagnoses peaked during March and April, which coincided with a surge in testing efforts, and then plateaued (Fig. 1). The median age of the case patients was 34 years (interquartile range, 28 to 42), 57.5% were men, 98.9% were white, and 89.5% resided in Scott County (Table 1); the estimated prevalence of HIV among adults, 18 to 65 years of age,

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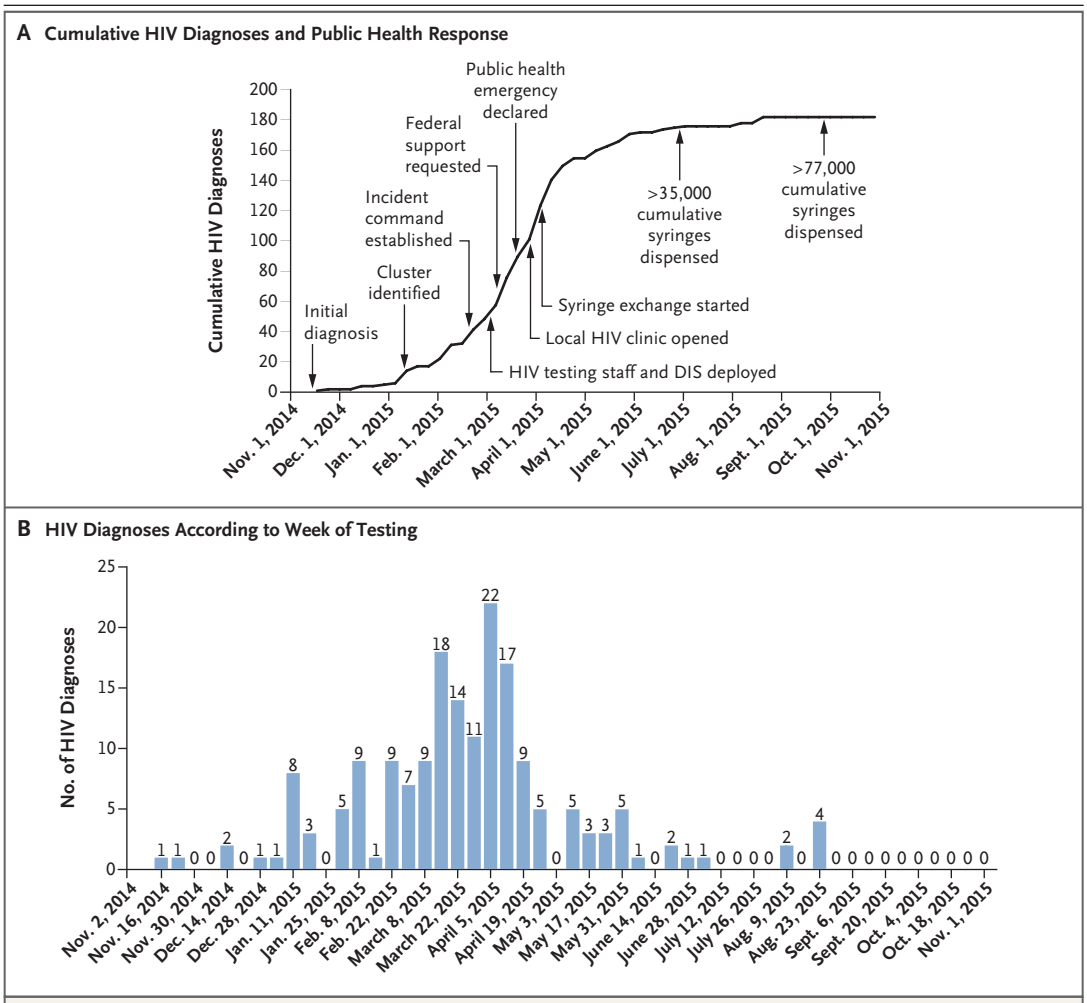

Figure 1. Outbreak of HIV Infection in Southeastern Indiana.

Panel A shows the cumulative number of human immunodeficiency virus (HIV) infections associated with injection of the prescription opioid oxymorphone and the public health response, according to the date of diagnosis. DIS denotes disease intervention specialist. "Incident command established" indicates that the state health department used a standardized approach to the command, control, and coordination of the emergency response. Panel B shows the HIV diagnoses that were associated with injection of the prescription opioid oxymorphone among 180 patients, according to the week of testing. One patient was later determined to have received a diagnosis of HIV infection before the outbreak period and was excluded.

in Scott County at that time was 1.1%. A total of 159 of the 181 case patients (87.8%) reported injecting the prescription opioid oxymorphone in the previous 12 months (91.9% of the 173 case patients who reported injection-drug use). Persons who reported injecting oxymorphone frequently described crushing, dissolving, and cooking extended-release oxymorphone (Opana ER, Endo Pharmaceuticals). Case patients also reported injecting other drugs in the previous 12 months; among the 173 case patients who reported injection-drug use, 47 (27.2%) reported occasionally injecting heroin, 40 (23.1%) reported injecting methamphetamine, 15 (8.7%) reported injecting cocaine, and 2 (1.2%) reported injecting oxycodone. Among 77 female case patients, 19 (24.7%) reported exchanging sex for money or drugs in the previous 12 months. Overall, 167 case patients (92.3%) were coinfected with HCV, which included diagnoses that were made before and during the outbreak (Table 1).

MOLECULAR ANALYSIS

Molecular analysis of the HIV-1 *pol* gene in 159 case patients who had available blood specimens revealed two clusters of HIV-1 subtype B infec-

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tion: cluster 1 comprised 157 sequences (98.7%) and cluster 2 comprised 2 sequences (Fig. 2). A subgroup of 48 sequences with 100% nucleotide identity was found within cluster 1. The 2 case patients who had sequences in cluster 2 reported no injection-drug use and were also not linked epidemiologically to the case patients who had sequences in cluster 1. Reference sequences obtained from surrounding counties in Indiana and those that were identified in the GenBank database search were not closely related to the sequences in the first cluster, a finding that is consistent with the outbreak being confined to Scott County. No major genotypic mutations that cause drug resistance were detected in any sequence. Among 125 case patients who had blood specimens available for recency testing, 113 (90.4%) had infections that were classified as recent (defined as infection in the previous 221 days). Among 113 case patients who had detectable HCV antibody levels and had blood specimens available for HCV molecular testing, 76 (67.3%) had detectable HCV RNA levels consistent with active HCV infection. Genotyping was performed on the sequences found in 67 of the 76 blood specimens, and the results showed that the most common genotype was genotype 1a (50 sequences, which included a unique cluster of 28 sequences and an additional 22 sequences that did not cluster), followed by genotype 3a (14 sequences, all of which formed a single cluster phylogenetically) and genotype 2b (3 sequences that did not cluster).

CONTACT TRACING INVESTIGATION

As of November 1, 2015, disease intervention specialists had identified 536 unique persons who were named as contacts by the 181 case patients; 468 (87.3%) of these contacts were located, assessed for risk, and tested for HIV infection (Fig. 3). A total of 287 contacts were found to be negative for HIV. In the 14 days preceding November 1, 2015, no new contact was named during the partner services investigations. The HIV-infected case patients and the contacts who were negative for HIV did not differ with respect to age (median age, 34 and 35 years of age, respectively; P=0.82) or sex (58% men and 56% men, respectively; P=0.76). The HIV-infected case patients were more likely to be named as syringe-sharing partners than were the contacts who were HIV-negative (81% vs. 52%, P<0.001) and were less likely to be named as a sexual

Table 1. Demographic and Clinical Characteristics and Risk Behaviors of HIV-Infected Persons — Southeastern Indiana, November 18, 2014, to November 1, 2015.*

Variable	Patients (N=181)
Demographics	
Age — no. (%)	
<25 yr	26 (14.4)
25–34 yr	71 (39.2)
35–44 yr	55 (30.4)
≥45 yr	29 (16.0)
Median age (interquartile range) — yr	34 (28–42)
Sex — no. (%)	
Male	104 (57.5)
Female	77 (42.5)
Race — no. (%)†	
White	179 (98.9)
Other or missing data	2 (1.1)
County of residence — no. (%)	
Scott County	162 (89.5)
Other county	19 (10.5)
Risk behaviors	
Injection-drug use — no. (%)	173 (95.6)
Reported link to a partner with HIV infection — no. (%)	
Sex only	1 (0.6)
Syringe sharing only	67 (37.0)
Sex and syringe sharing	97 (53.6)
No reported link	16 (8.8)
Female patients engaged in commercial sex work — no./total no. (%)	19/77 (24.7)
Male patients having sex with men — no./total no. (%)	8/104 (7.7)
HIV clinical characteristics	
Baseline HIV-1 viral load — no./total no. (%)	
<10,000 copies/ml	11/153 (7.2)
10,000–100,000 copies/ml	46/153 (30.1)
100,001–1,000,000 copies/ml	91/153 (59.5)
>1,000,000 copies/ml	5/153 (3.3)
Median HIV-1 viral load — copies/ml	147,820
Interquartile range	48,763–369,763
Full range	70–10,000,000
Baseline CD4 cell count — no./total no. (%)	
<200 cells/mm^3	3/143 (2.1)
200–500 cells/mm^3	39/143 (27.3)
>500 cells/mm^3	101/143 (70.6)
Median CD4 cell count — cells/mm^3	628
Interquartile range	446–809
Full range	17–1400
Other clinical characteristics — no./total no. tested (%)	
Hepatitis C virus coinfection‡	167/181 (92.3)
Reactive for hepatitis C virus RNA	76/113 (67.3)
Reactive for hepatitis B virus surface antigen§	7/86 (8.1)
Reactive rapid plasma reagin test§	2/77 (2.6)

* HIV denotes human immunodeficiency virus.
† Race was self-reported.
‡ Coinfection with hepatitis C virus was defined as a reactive test result for antibodies to hepatitis C virus.
§ Case patients with detectable hepatitis B virus surface antigen were referred for care, and case patients with a reactive rapid plasma reagin test were treated.

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partner only (1% vs. 15%, P<0.001). Among the 287 contacts who were negative for HIV, 183 (63.8%) were tested for HCV infection, of whom 116 (63.4%) were found to be positive (see the Supplementary Appendix).

We analyzed a subgroup of 196 contacts who had been named by an HIV-infected case patient as a syringe-sharing partner and for whom information on risk behavior was collected at the time of HIV testing. The HIV-infected contacts and the contacts who were negative for HIV infection were similar with respect to the rates of poverty (defined as an annual income <$10,000) (93% and 90%, respectively; P=0.43) and incarceration in the previous year (53% and 56%, respectively; P=0.64) (Table 2). In this subanalysis, HIV-infected contacts were also more frequently named as syringe-sharing partners by HIV-infected case patients than were the contacts who were negative for HIV (median times named, 4 vs. 1; P<0.001; adjusted risk ratio for each time named, 1.9; P<0.001).

Figure 2 (facing page). Maximum-Likelihood Phylogenetic Tree of HIV-1 Polymerase Sequences — Southeastern Indiana, November 18, 2014, to November 1, 2015.

This figure diagrams the maximum-likelihood phylogenetic relationships of 159 HIV-1 polymerase (*pol*) sequences from case patients in southeastern Indiana who received a new diagnosis of HIV infection between November 18, 2014, and November 1, 2015, and who had a specimen available for sequencing (red-filled circles); the diagram also includes local reference *pol* sequences from HIV infections diagnosed in Indiana counties other than Scott County (open red circles) and GenBank reference sequences identified with the use of Basic Local Alignment Search Tool (BLAST) software (black-filled circles). Branches of some reference sequences are collapsed (black-filled triangle) for better visualization of the complete tree, and the number of taxa in that branch are shown. Rooting of the tree was performed with the use of reference HIV-1 group M subtype C and J sequences. Confidence values for the branching pattern were assessed with the Shimodaira–Hasegawa test and are given as probabilities to the left of each branching node. The unit for the scale bar of 0.02 (solid line at bottom) is the number of nucleotide substitutions per nucleotide site. The phylogenetic analysis identified 157 sequences that formed a cluster (cluster 1; red-filled triangle opening to the box on the right), which was highly related (mean nucleotide identity, 99.7%). No Indiana or GenBank reference sequence was closely related to cluster 1.

SUMMARY OF OUTBREAK RESPONSE

In response to this outbreak, a public health emergency was declared on March 26, 2015, in a state of Indiana executive order (Fig. 1A).[29,30] Response efforts included the rapid expansion of free HIV and HCV testing and partner services, establishment of local HIV treatment services, provision of access to substance-use disorder treatment services, immediate access to health insurance, immunization services, executive governmental actions (Executive Order 15-05), and general public education components (Table S1 in the Supplementary Appendix). The number of HIV tests performed increased from 23 tests in November 2014 to 1838 tests between March 1 and May 31, 2015 (>600 tests per month). The percentage of test results that were reactive declined from 7.7% in March to 5.7% in April to 0.8% in May. HIV screening among 582 inmates in eight county jails adjacent to Scott County identified two HIV infections (0.3%) that were phylogenetically and epidemiologically linked to the outbreak. In addition, pooled RNA testing identified three additional HIV-1 diagnoses (0.7%) in 429 specimens that tested negative for HIV antibody.

By March 31, 2015, the local medicine practice, with the support of specialists in infectious diseases, had initiated HIV care in this community. Between April 4 and November 1, 2015, among 176 patients with HIV infection who could be monitored (i.e., they were alive and residing in Indiana), 152 (86.4%) attended an HIV medical care appointment and 107 (60.8%) initiated therapy with antiretroviral medications. By April 4, 2015, the local health department had established an emergency syringe-exchange program (the first syringe exchange in the state of Indiana). During the period from April 4 to October 31, 2015, a total of 277 persons who injected drugs enrolled in the program, and more than 97,000 sterile syringes were distributed and returned. The persons in the syringe-exchange program reported a median of 5 injections per day (interquartile range, 2 to 15).

DISCUSSION

In this outbreak of HIV infections, the introduction of a single HIV-1 strain resulted in an explosive transmission of HIV within a densely connected network of persons who injected drugs and who shared syringes to inject the extended-

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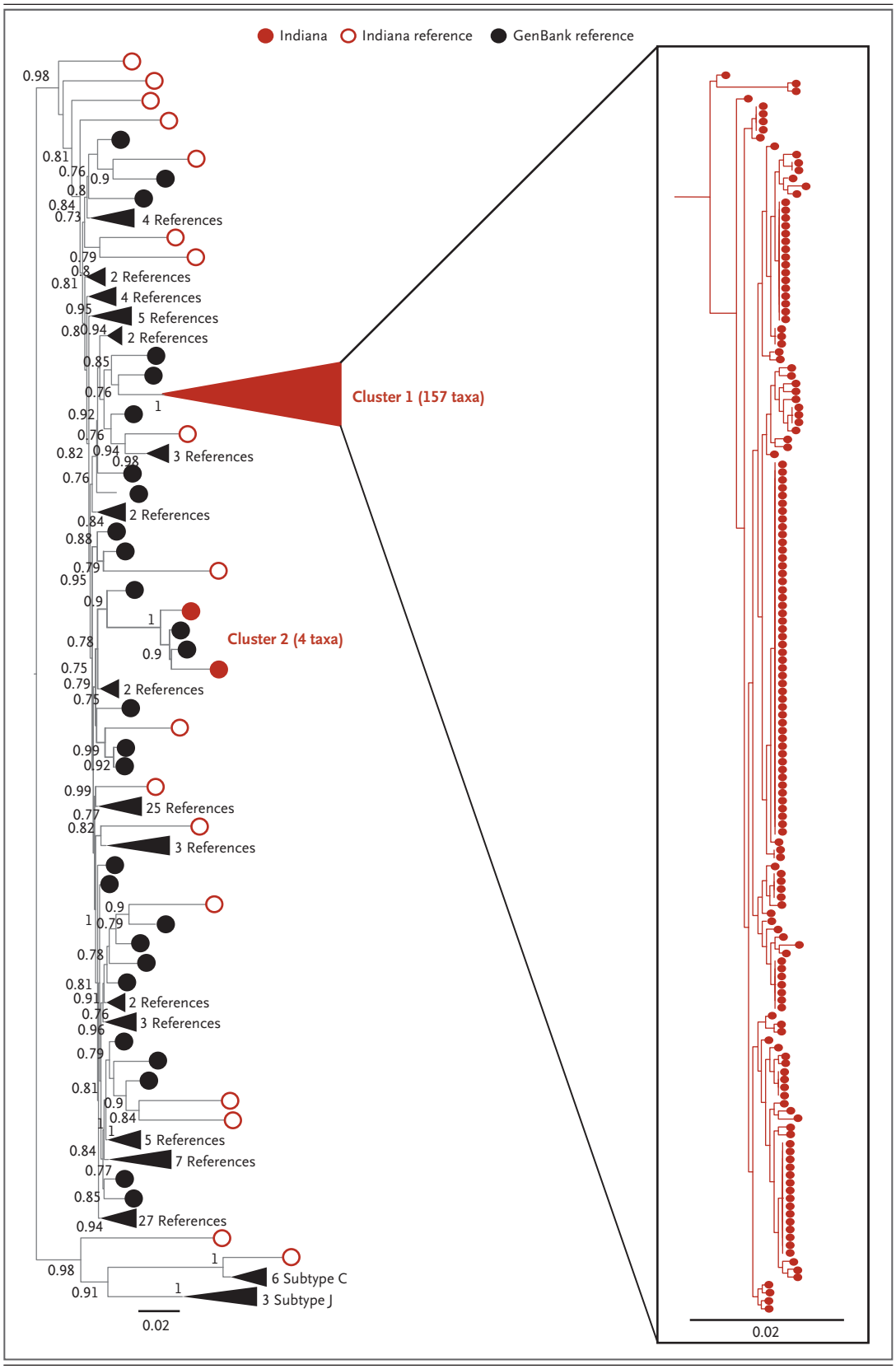

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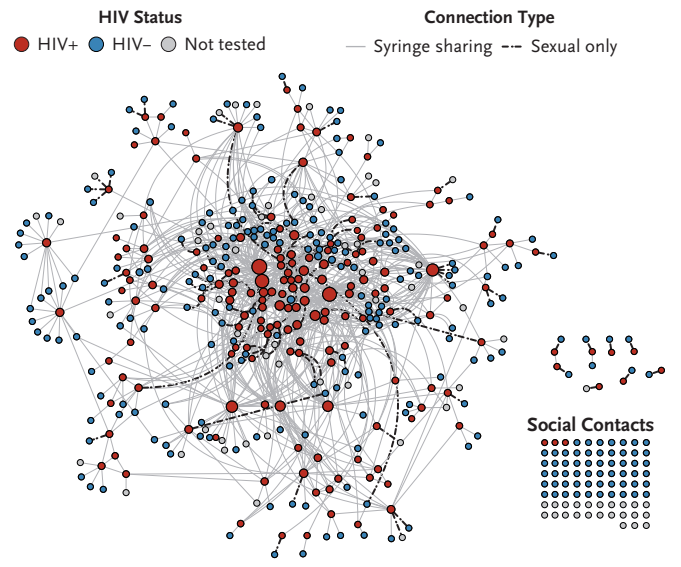

Figure 3. Syringe-Sharing Network of Persons with Newly Diagnosed HIV Infection.

This figure diagrams the network of 181 case patients in southeastern Indiana who received a new diagnosis of HIV infection between November 18, 2014, and November 1, 2015; the network is based on the syringe-sharing and sexual partners of the case patients at the time of their HIV diagnosis. The network comprises 536 unique persons and 1058 unique connections: 841 of the contacts in this network (79.5%) were syringe-sharing contacts, 81 (7.7%) were sexual contacts only, and 136 (12.8%) were syringe-sharing and sexual contacts. Reported contacts are represented by circles colored to reflect HIV status, and the sizes of the circles are proportional to the number of connections, with larger circles indicating more connections (range of number of connections, 1 to 56). Connections are represented by a solid gray line if the contact was a syringe-sharing contact only or a syringe-sharing and sexual contact and by a dashed black line if the contact was a sexual contact only. The 83 "social contacts" in the bottom right are persons with no reported syringe-sharing or sexual connections to other members of the network. These social contacts were named by case patients as persons the case patients knew who could benefit from an HIV test.

release formulation of the prescription oral opioid oxymorphone. This outbreak prompted the state to declare a public health emergency that facilitated a rapid, multitiered public health response that included immediate access to health insurance and HIV care and treatment, as well as the creation of a syringe-exchange program, in response to this HIV and HCV outbreak, that had previously been illegal under Indiana state law. Abuse and injection of prescription opioid analgesics was the root cause of this HIV outbreak, and these issues affect many communities.

The features of this outbreak offer several insights that may help prevent similar events in the future. First, the initial patients were detected during routine HIV screening and by an alert disease intervention specialist. This rapid detection highlights the importance of supporting and expanding critical public health services, especially HIV testing in rural communities in which the incidence of HIV is very low but injection-drug use related to the expanding opioid epidemic has disproportionately increased.[31] Second, the size of the network of persons who inject drugs and the extent of syringe sharing was unexpected, given the small population of the town. However, large networks of persons who inject drugs have been observed in other communities of similar size,[9,11] which shows that such networks can be present in sparsely populated rural areas. Third, HCV infection was highly prevalent in this network of persons who inject drugs. Reports of new HCV infections should be noted because they can serve as markers of communities at risk for HIV, and interventions to prevent further HCV infections, such as syringe-exchange programs, could possibly contribute to reducing the risk of an HIV outbreak.[32]

A lack of health insurance could have been a barrier to the response to this outbreak, but fortuitously, in January 2015, Indiana received a waiver to provide Medicaid insurance under the Healthy Indiana Plan (HIP 2.0).[33] HIP 2.0 helped to ensure health care coverage in the largely uninsured and impoverished community that was affected by the outbreak and facilitated the immediate enrollment, coverage, and access to critical health care services, including HIV treatment. Even with access to health insurance, a local HIV treatment provider, and care coordination, there were substantial challenges to the rapid initiation of therapy with antiretroviral medications.

The circumstances underlying this HIV outbreak are not unique to this community. Although the magnitude of the outbreak was alarming, the introduction of HIV into a rural community in the United States was not unexpected when considered in the context of increasing trends in injection use of prescription opioid analgesics[1,4,7,9,11,14,34] and the new and steady rise in acute HCV infections in rural areas, particularly central Appalachia.[15] In addition, although approximately 50% of the persons who inject drugs in the United States are estimated to live outside major metropolitan areas, only an estimated 5.8% of syringes were exchanged in

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Table 2. Characteristics and Risk Behaviors of Persons Named as Syringe-Sharing Partners during Partner Services Investigations, According to HIV Status — Southeastern Indiana, November 18, 2014, to November 1, 2015.*

Variable	All (N=196)	HIV-Positive (N=100)	HIV-Negative (N=96)	P Value
Male sex — no. (%)	113 (57.7)	58 (58.0)	55 (57.3)	0.92
Median age (interquartile range) — yr	33 (27–41)	32 (27–40)	34 (26–42)	0.82
Non-Hispanic white — no. (%)	193 (98.5)	100 (100)	93 (96.9)	0.07
Annual income <$10,000 — no./total no. (%)	158/172 (91.9)	85/91 (93.4)	73/81 (90.1)	0.43
Incarcerated in past year — no./total no. (%)	104/192 (54.2)	52/99 (52.5)	52/93 (55.9)	0.64
Previously tested for HIV — no./total no. (%)	96/192 (50.0)	45/98 (45.9)	51/94 (54.3)	0.25
Reported injection-drug use — no. (%)	166 (84.7)	89 (89.0)	77 (80.2)	0.09
Shared drug-injection equipment — no. (%)	138 (70.4)	75 (75.0)	63 (65.6)	0.15
Sex without a condom — no. (%)	167 (85.2)	86 (86.0)	81 (84.4)	0.75
Sex with persons who exchange sex for money or drugs — no. (%)	18 (9.2)	11 (11.0)	7 (7.3)	0.37
Sex for money or drugs — no. (%)	17 (8.7)	9 (9.0)	8 (8.3)	0.87
Sex while on drugs — no. (%)	125 (63.8)	66 (66.0)	59 (61.5)	0.51
Sex with persons who inject drugs — no. (%)	125 (63.8)	68 (68.0)	57 (59.4)	0.21
Sex with HIV-infected persons — no. (%)	44 (22.4)	28 (28.0)	16 (16.7)	0.06
Sex with men who have sex with men — no. (%)	2 (1.0)	0	2 (2.1)	0.14
Median no. of times named as syringe-sharing partner (interquartile range)	2 (1–4)	4 (2–6)	1 (1–2)	<0.001

* Risk behavior during the previous 12 months was self-reported by the syringe-sharing partners with the use of a check box. The P values indicate whether the proportion of HIV-infected persons who selected that risk behavior differed from the proportion of HIV-negative persons who selected that risk behavior.

rural locations.[35] Resources related to the prevention and treatment of HIV did not exist in this community before the outbreak, and, as in many rural communities, access to basic health care, substance-abuse treatment, and HIV prevention services was limited.[36]

Proactive public health interventions are needed to prevent or limit future HIV outbreaks in similar communities and should be designed on the basis of an integrated model that combines HIV and HCV testing and prevention education efforts with the use of antiretroviral medications for HIV treatment and preexposure prophylaxis, syringe-service programs, and treatment of substance-use disorder with medication-assisted treatment[37] (additional details are provided in the Supplementary Appendix). Substantial barriers to syringe exchange (i.e., laws prohibiting syringe exchange or syringe possession, lack of funding or of a community organization to implement the syringe exchange, and stigma) existed in this community before this outbreak. Although overcoming these barriers may be challenging outside the context of an emergency response, recent changes in federal[38] and state[39] laws related to syringe exchange have created new opportunities to increase access. To prevent the expansion of HIV into rural networks of persons who inject drugs throughout the United States, it will be necessary to overcome these barriers to syringe exchange[32] and opioid-replacement therapy,[40] strategies that are associated with a 56% and 64% reduction, respectively, in the risk of HIV infection.

The findings of this investigation may not necessarily be generalizable to networks of persons who inject drugs who live in other communities at risk. In this outbreak, the persons who injected drugs preferentially used extended-release oxymorphone, the pharmacokinetic properties of which differ from those of other opiates and may be associated with more frequent injections and sharing of injection equipment among several persons (further details are provided in the Supplementary Appendix). In addition, the community of persons who injected drugs in this outbreak was relatively isolated from sur-

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rounding communities; only 10% of the persons who received a diagnosis of HIV infection resided outside Scott County, and all these persons had epidemiologic links to Scott County, most often through having used drugs in Scott County, according to their reports. This geographic confinement limited the spread of this outbreak to surrounding counties but may not be representative of networks of persons who inject drugs in other rural areas.

In conclusion, this outbreak highlights the vulnerability of the growing numbers of persons who inject drugs in rural communities to the introduction and rapid transmission of HIV, as well as other bloodborne pathogens such as HCV and HBV. Although the proactive deployment of interventions for HIV prevention among persons who inject drugs is challenging in rural areas that have a low incidence of HIV but are at risk for an outbreak, the implementation of HIV testing and treatment, syringe-service programs, and medication-assisted treatment are necessary to help prevent a similar outbreak in the future.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC). The use of trade names and commercial sources is for identification only and does not imply endorsement by the CDC.

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